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RECENT DEVELOPMENTS IN DIGITALIS

This review of the subject of digitalis is presented with the object of bringing together a few of the more recent developments in our knowledge of this group of drugs.

Mechanism of Action in Heart Failure. There has been considerable controversy in relation to this matter. One of the most popular views holds that digitalis exerts a primary action on the "tone" of the heart muscle. There is no general agreement as to the nature of the property called "tone," but it is usually measured as the resting length of the muscle or the diastolic size of the heart. The complex nature of the mechanisms prevailing in the intact animal or human makes it impossible to obtain in them entirely conclusive evidence as to whether the change in 'tone" is primary or secondary. Recent experiments which were carried out with a preparation of the mammalian papillary muscle throw new light on this question. By means of this preparation it is possible to differentiate between the action of the drug on "tone" and on systolic force. In such experiments it has been found that digitalis preparations in concentrations similar to those which prevail after therapeutic doses in man produce an increase in the force of the contraction of the heart muscle without any effect on "tone," that is, without any effect on the resting length of the heart muscle. The systolic force which is allowed to decline to a fraction of the normal (heart failure) is restored to normal shortly after the administration of the drug. In these experiments it has also been possible to exclude other mechanisms such as changes in rate, in coronary circulation, and in return flow, all of which indirectly influence the diastolic size of the heart.

Further light is thrown on the details of the mechanism by which systolic force is increased in the experiments of Visscher and his collaborators who found that digitalis increases the efficiency of the heart muscle, that is, it increases the amount of work which the heart muscle can do for a given expenditure of energy, and in the experiments of Cattell which suggest that the increased force may result from a change in the calcium-potassium ratio in heart muscle since, under the influence of digitalis, heart muscle loses potassium.

Mechanism of Cardiac Slowing. The mechanism by which digitalis slows the heart rate in auricular fibrillation has received some clarification in experiments on humans. Cushny in 1912 maintained it was chiefly an action directly on A-V conduction. About 10 years later Lewis took the position, on the basis of his experiments, that it was chiefly an action through the vagus, and about 10 years thereafter Porter wrote that the action was entirely through the vagus. The more recent experiments show that in patients with auricular fibrillation digitalis maintains the ventricle at a slow rate usually by the summation of two factors, one a vagal factor which is abolished by atropine and the other an extravagal factor not abolished by atropine. This is of some importance in connection with the problem of controlling the ventricular rate in patients with auricular fibrillation. Some of the patients who appear to be satisfactorily digitalized and maintain a slow heart rate when they are at rest, show extreme acceleration of the heart during free physical exercise. It is the cause of considerable discomfort, with shortness of breath and a sense of palpitation. Digitalization sufficient to invoke the extravagal mechanism prevents the marked acceleration of the heart during physical effort in most patients with auricular fibrillation. In this state free physical exercise will not often accelerate the ventricular rate above 100 a minute.

Dosage is the deciding factor. After smaller doses, the vagal mechanism predominates; after larger doses, the extravagal. In some cases the dose which

IMPORTANT NOTICE

The Eighteenth Scientific Meeting of the American Heart Association will be held at Hotel CHALFONTE-HADDON HALL, Atlantic City, N. J. The general cardiac program will be given on Friday, June 5, and the program of the Section for the Study of the Peripheral Circulation on Saturday, June 6.

Admission to meetings will be free to all 1942 paid-up members, upon presentation of their membership card.

To *non-members*, a registration fee of $2.00 will be charged.

establishes the extravagal mechanism is quite close to that which induces impairment of appetite and nausea.

Potency of Digitalis. It is well known that the potency of different specimens of digitalis varies. About 35 years ago Edmunds assembled preparations of digitalis on the American market. He tested them biologically in frogs and found that the strongest was about 3 times as potent as the weakest. Biological standardization of digitalis was not in general use at that time. As a result of these and other observations, the U.S. Pharmacopeia adopted the frog method for the assay of digitalis. The object was to insure digitalis of uniform potency in man. Many other methods for the assay of digitalis have since been devised. The cat method became very popular in this country and several outstanding preparations were assayed by this method. The experiment which Edmunds made with market preparations in 1907 was repeated in 1940 by the group at Cornell in order to determine whether digitalis tinctures on the market at this time were in fact more uniform than they used to be. In these tests the cat method of Hatcher was employed. The results were rather startling. They showed that the outstanding tinctures on the market at the present time show wide variations in potency, and the strongest is still about 3 times as potent as the weakest. These are all labeled U.S.P. XI Tincture Digitalis, hence supposedly of similar potency by the frog method. It is clear, therefore, that the frog and the cat methods give different answers in the standardization of digitalis. Two specimens may be of the same potency by the cat method, while one may be twice as strong as the other when tested by the frog method. The essential question was, which method gives results more nearly applicable to man? A series of experiments were recently published in which the results of the two methods of assay were applied to humans, in patients with heart failure and auricular fibrillation. The outcome of these studies indicates that the frog is not a suitable animal for the standardization of digitalis preparations, and that when the frog and the cat method give different answers in a comparison of specimens of digitalis, that obtained with the cat method is more nearly applicable to humans. The cat method has now been adopted as the official method of assay for the forthcoming Twelfth Revision of the U.S. Pharmacopeia. It is to be expected that in the future the potency of digitalis preparations on the market will be more uniform.

There are certain objections to the cat method as well, since the technique involves intravenous injection and in that way the cat method fails to distinguish between absorbable and non-absorbable material. This is a matter of some importance, since digitalis is most commonly administered orally in man. In more recent studies an endeavor has been made to develop a method of assay of digitalis directly on humans. A large measure of success has been attained and some preparations of digitalis are now being provided in commerce, the uniformity of which is assured by direct standardization on humans.

Closely related to the matter of bio-assay of digitalis is the belief that digitalis leaf and the tincture deteriorate. It has been shown repeatedly by the frog method that when the tincture of digitalis (and probably also the leaf) is stored for months, it loses potency. However, we appear to have been misled by the method by which the loss of potency was revealed. After a tincture is stored for about 3 or 4 months it may lose as much as 50 per cent of its previous potency as revealed by the frog test. But, by the cat test, the tincture retains its previous strength. The explanation of this is not clear. It may be that upon standing, the potent glycosides in the tincture undergo some form of physical change which alters their absorption from the lymph sac of the frog, although in this form it retains its full potency when injected intravenously in cats. Tests in humans, made with a very old tincture which had "deteriorated" by the frog method, showed full strength in humans.

Preparations. In the choice of a preparation of digitalis one of the questions that arises is whether the quality of action of one differs from that of another. If one preparation fails to produce satisfactory therapeutic effects, assuming that it has been absorbed and that the dose has been large enough, is it likely that some other preparation of digitalis will accomplish more? That question arises particularly in connection with the treatment of patients in advanced heart failure whose response to digitalis materials is often incomplete or equivocal. There are statements in the literature to the effect that the quality of action of different digitalis glycosides is not the same, and from some of the more recent experiments with heart-lung preparations, the conclusion has been drawn that the margin between therapeutic and toxic effects on the heart is much wider for some than for other glycosides. The existing evidence for this view leaves much to be desired. No significant difference in the margin between toxic and therapeutic doses of a wide variety of digitalis glycosides could be observed in the experiments on the mammalian papillary muscle. The subject has also been studied directly in man and here also the margin of safety between the therapeutic and toxic dose has been found to be substantially similar for digitalis, Lanatoside-C and digitoxin (Digitaline Nativelle).

The view that strophanthin by intravenous injection produces effects which cannot be obtained with digitalis has been popular in the European literature for many years, and has recently been revived in this country. No good evidence exists that this is so, provided suitable measures have been taken to insure that adequate doses of digitalis have reached the circulation.

The purified glycosides of digitalis have come in for a good deal of attention in recent years. A pure principle which is rapidly absorbed from the gastrointestinal tract and which does not need to be as-

sayed by biological methods is the objective of chemical research in digitalis materials. Interesting developments have occurred in this field. Several relatively pure glycosides have been prepared and are now available for general use.

Ouabain is a pure glycoside which has long been in use and has now been included in the Twelfth Revision of the U.S. Pharmacopeia. It is very poorly absorbed from the gastrointestinal tract. It is therefore suitable only for intravenous or intramuscular injection. An intravenous injection of 0.25 mg. repeated once or twice at intervals of 2 hours will produce dramatic relief of the symptoms of heart failure, and in patients with auricular fibrillation will reduce the heart rate from a level of 150 to 70.

One of the outstanding members of the newer group is Lanatoside-C (from digitalis Lanata). It supplies a useful substitute for ouabain for intravenous and intramuscular injection, the full digitalizing dose by intravenous injection being from 1.5 to 2 mg. Its absorption from the gastrointestinal tract, however, is also quite imperfect. It requires about 10 times as much by oral administration as by intravenous injection to produce similar effects. The purified mixtures of digitalis glycosides such as Digifoline have been widely used and have filled a need especially in relation to parenteral administration. However, emphasis should be placed on the fact that oral administration of digitalis meets the needs satisfactorily in the vast majority of cases, and the indiscriminate use of digitalis preparations by parenteral administration is to be discouraged.

One of the older glycosides which has been very popular abroad for many years but relatively neglected in this country, namely, digitoxin (Digitaline Nativelle), has recently been subjected to more intensive study here in animals and in man. It possesses a property quite unique for a digitalis body, that of complete absorption from the gastrointestinal tract, as seen from the fact that the average oral and intravenous doses for full digitalization in man are practically identical, namely, 1.25 mg. This represents a total of 3 cat units.

In this connection it should be noted that 3 cat units of this material produce the effects of about 15 cat units of digitalis leaf or tincture, a fact which in turn indicates that the absorption of digitalis leaf or tincture is not nearly as complete as is commonly supposed. It is probable that not more than about one-fifth of the potent materials in digitalis play a part in the therapeutic effect of the drug when administered by mouth. The rest represents probably non-absorbable material.

This brings up another matter of some practical interest, namely, the fact that the full digitalizing dose of digitalis by mouth and by vein are not the same. While it requires approximately 15 cat units to induce full therapeutic effects with digitalis by mouth, only about 3 cat units are required by intravenous injection. This ratio has been observed in the study of patients with auricular fibrillation in which comparisons were made with the two methods of administration in one and the same patient. For this purpose purified preparations of the whole leaf were used so that the same material was given by mouth and by vein. Included among these was the preparation of commerce known as Digifoline. It is not to be assumed that all patients can be fully digitalized by 3 cat units of a digitalis material by vein. Some require as much as 6 cat units. Individual variation in susceptibility to digitalis is a well known phenomenon. What needs to be stressed, however, is the fact that to produce a similar degree of effect, it requires approximately 5 times as much potent material by mouth as by vein in the case of digitalis or purified materials representing essentially the mixture of glycosides present in the whole leaf.

Dosage. Several matters relating to dosage have already been considered. Just a word in regard to the relation of the plan of dosage to the speed of digitalization. It is customary to take a day or two or longer to induce the full effects of digitalis. The full dose, whatever it is estimated to be, 1 gram or 1.5 grams for a given individual, is divided into 4 or 5 fractions and given at 6 or 8 hour intervals. It is not essential to give it all at one time, since the average patient with heart failure is not in extremis and little is lost by taking 2 or 3 days rather than 6 or 8 hours to induce the full effects. However, the chief reason for the divided doses is the fact that from a single full dose poisoning may result in the more susceptible individuals. Since varying susceptibility as measured by oral doses includes the factor of varying absorption, it was considered that digitoxin-like material which is rapidly and, for practical purposes, completely absorbed from the gastrointestinal tract, might provide a means of safe full digitalization by a single dose method. This was found to be the case with digitoxin (Digitaline Nativelle). The average full digitalizing dose of 3 cat units (1.25 mg.) may be given at one time to the patient with heart failure who has not recently received digitalis. It induces the full effects within a period of about 6 to 10 hours, sometimes more quickly. One out of 50 patients develops nausea or vomiting under these conditions.

Digitalis leaf or the tincture will not take the place of digitoxin (Digitaline Nativelle) in the single dose method of digitalization. Hatcher's classical experiments in animals and Eggleston's studies in man have amply demonstrated that digitalis emesis as commonly encountered is a result of systemic action after the drug has been absorbed. When a patient is digitalized with small repeated doses, a local emetic action is unusual. However, large doses exert a strong local emetic action. This action precludes the routine use of digitalis leaf or the tincture in the single dose method of digitalization, since with these, 1 out of 5 patients develops nausea or vomiting within less than 2 hours, and before any considerable part of the drug is absorbed.

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